08/846933

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/846,933	04/30/97	CLELAND J	P0825BC3

EXAMINER

18M1/1201

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ART UNIT	PAPER NUMBER
1802	4

DATE MAILED: 12/01/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on April 30, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 4-9 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1, 4-9 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

DETAILED ACTION

In this application:

Claims 1, 4-9 are now pending and under examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the earlier filed application(s) in the first sentence of the specification (37 CFR 1.78).

Drawings

The drawings in this application are objected to by the Draftsperson as informal. Any drawing corrections requested but not made in the prior application should be repeated in this application if such changes are still desired. If the drawings were changed and approved during the prosecution of the prior application, a petition may be filed under 37 CFR 1.182

requesting the transfer of such drawings, provided the parent application has been abandoned. However, a copy of the drawings as originally filed must be included in the 37 CFR 1.60 application papers to indicate the original content.

Claim Rejections - 35 USC § 112

Claims 1 and 4-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 the timing of the second and third phases of the triphasic pattern of antigen release is not clear because both the second and third phases have the same range of release (i.e. 1 to 180 days). Since no antigen may be released (0%) during the second phase, the release appears to be biphasic rather than triphasic. Therefore, although a triphasic response is recited in the claim, the timing of the release is not clearly set forth in the claim.

Claim 1 recites the limitations "the ratio of lactide to glycolide", "the inherent viscosity", "the median diameter".

However, there is insufficient antecedent basis for these limitations in the claim.

Claim 4 recites the limitation "the median diameter". However, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Alonso et al

Alonso et al (Pharmaceutical Research 10(7):945-953, 1993 July) disclose a composition comprising poly(lactic/glycolic) acid (PLGA) microspheres containing tetanus vaccine. Furthermore, Alonso et al disclose that the PLGA had a comonomer ratio of 50/50 and an inherent viscosity of 0.8.

Thus, the prior art disclosure is viewed as anticipating the claimed invention.

Claims 1, 4, and 9 are rejected under 35 U.S.C. 103 as being unpatentable by Eppstein et al.

Eppstein et al (US Patent #4,962,091) teach a composition comprised of poly(lactide-co-glycolide)(PLGA) with a molar ratio of lactide to glycolide units of 100:0 to 30:70, and an intrinsic viscosity from about 0.2 dl/g to about 1.5 dl/g. Eppstein et al also teach that the composition of PLGA can be used to deliver biologically active polypeptides to mammals. Furthermore, Eppstein et al teach that since the controlled release device produces only minor loss of biological activity of the polypeptides, the likelihood of undesirable immune responses at the site of polypeptide delivery is reduced. In addition, Eppstein et al teach that the system can be designed to deliver the active agent at an appropriate rate over prolonged periods of time ranging from less than one day to several months. (See especially column 2, lines 57-61; column 3, lines 32-41, and 60-63; column 4, lines 15-28; column 6; column 11; column 12, lines 31-46)

Although Eppstein et al do not teach a median diameter of the microspheres, the reference teaches that the rate and duration of release can be varied by the choice of polylactide polymer, molar ratio, intrinsic viscosity, and by the shape and configuration of the device. Therefore, absent evidence to the

contrary, the median diameter of the microsphere from about 20 to 100 um is considered routine experimentation.

Therefore, it would have been obvious to one of ordinary skill at the time the invention was made to encapsulate antigens within microspheres of various diameters, compositions, and viscosity in order to deliver the antigen for release at various rates and duration with a reduced likelihood of undesirable immune response at the site of delivery.

Claims 1, 4, 9, and 10 are rejected under 35 U.S.C. 103 as being unpatentable over Sanders et al in view of Eldridge et al (Mol. Immunol).

Sanders et al (J. Pharm. Sci 73(9):1294-1297, 1984) teach a composition comprised of poly (D-L-lactide-co-glycolide)(PLGA) microspheres and an encapsulated analogue of luteinizing hormone releasing hormone. (See especially pages 1294-1296).

Sanders et al also teach the microspheres having a ratio of lactide to glycolide of 69:31, an intrinsic viscosity of 9.97 dl/g, and a diameter in the range of 10-40 um. (See especially pages 1296, column 2, paragraph 2; legend of figure 6)

In addition, Sanders et al teach microspheres having a triphasic release over 90 days in which an initial burst is followed by a latent period of 25 days during which less than 0.4 ug/day of the analogue is released, followed by a final release from about day 38 to day 90 as the polymer erodes. (See especially Figure 4a and paragraph bridging pages 1296 to 1297).

It is noted that the 69:31 molar ratio taught by Sanders et al is equivalent to a 2:8:1 weight percent ratio of lactide:glycolide based on molecular weights of 144.12 and 116.07 for lactide and glycolide, respectively. Sanders et al, however, do not specifically teach the incorporation of an antigen in the microspheres nor do Sanders et al teach a use of the microspheres as vaccine, or the antigen encapsulated in the microspheres in addition to a soluble antigen.

Eldridge et al (Mol. Immunol 28(3):287-294, 1991) teach the use of poly D-L-lactide-co-gylcolide microspheres as a vaccine delivery system. Eldridge et al also teach that the copolymer has a history of safe application in man and has exceptional stability. Eldridge et al teach that in the case of mucosal immunization via oral or intratracheal application, the copolymer protects the antigen from degradation and targets delivery to the mucosally-associated lymphoid tissues. Eldridge et al teaches

that an advantage of the copolymer microcapsule delivery system is the ability to control the time and/or rate at which the incorporated material is released which allows for scheduling of the antigen release in such a manner as to maximize the antibody response following a single administration. Furthermore, Eldridge et al teach that the antigen can be released in a manner analogous to conventional primary and booster immunizations. (See especially page 288, column 1, paragraph 2; page 290, column 2, second paragraph).

Given the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the analogue of luteinizing hormone releasing hormone in the microspheres (as taught by Sanders et al) with an antigen (as taught by Eldridge) since the art teaches that antigens can be released from the PLGA microspheres.

Claims 5-7 are rejected under 35 U.S.C. 103 as being unpatentable by Sanders et al in view of Eldridge et al, and further in view of Wang et al.

The teachings of Sanders et al, and Eldridge et al were set forth above. It would have been obvious to substitute the analogue of luteinizing hormone releasing hormone in the microspheres taught by Sanders et al with an antigen as disclosed by Eldridge et al and to sue the composition as a vaccine for the reasons discussed above.

The references, however, differ in not teaching the microsphere composition with an adjuvant.

Wang et al (J. Controlled Release 17:23-32, 1991) teach that PLGA microspheres in which bovine serum albumin (BSA) and the adjuvant Carbopol 951 were encapsulated had a higher burst effect release of the BSA and a higher daily release of BSA than the microspheres without Carbopol 951. Wang et al also teach that Carbopol 951 was incorporated as a potential adjuvant and to enhance protein loading. (See especially page 28, Figure 4a; page 29, columns 1 and 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate and adjuvant in the antigen-encapsulated microspheres taught in the prior art because the adjuvant would be expected to enhance the immune response of the vaccine composition and may also have the

added advantage of a higher initial release of the antigen and more efficient protein loading as taught by Wang et al.

Claim 8 is rejected under 35 U.S.C. 103 as being unpatentable by Sanders et al in view of Eldridge and further in view of Wang et al (as applied to claims 1, 4-7, and 9) and further in view of Newman et al.

The teachings of Sanders et al and Eldridge et al and Wang et al were set forth above. It would have been obvious to substitute the analogue of luteinizing hormone releasing hormone in the microspheres taught by Sanders et al with an antigen as taught by Eldridge et al and to use the composition as a vaccine for the reasons discussed above. It would have been also obvious to include an adjuvant in the composition for the reasons discussed above.

The references, however, differ in not teaching the use of QS21 as the adjuvant.

Newman et al teach that QS21 has the advantages of augmenting both antibody responses and cell-mediated immunity and established immunological memory. Newman et al also teach that QS21 is non-toxic in macaques. (See especially pages 146, column 2; and page 1417, paragraph 1)

Given the teachings of the prior art that QS21 is non-toxic and augments both antibody responses and cell-mediated immunity, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include QS 21 as an adjuvant in the vaccine composition taught by the above cited references since QS21 can be used as a safe adjuvant in vaccine compositions for establishing immunological memory.

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1802.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to V. Ryan whose telephone number is (703)305-6558.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted to the Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). The fax number for Art Unit 1802 is (703)308-4242.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4017.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**james.housel@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

V. Ryan
Patent Examiner/Art Unit 1802
November 1997
Ryan/vr

VR

James C. Housel 11/24/97
JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER
GROUP 180